



PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference L2BD29/LB/2	FOR FURTHER ACTION See Form PCT/IPEA416	
International application No. PCT/EP2004/007606	International filing date (day/month/year) 08.07.2004	Priority date (day/month/year) 08.07.2003
International Patent Classification (IPC) or national classification and IPC C12N15/00		
Applicant UMC UTRECHT HOLDING B.V. et al.		
<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 10 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input checked="" type="checkbox"/> sent to the applicant and to the International Bureau a total of 7 sheets, as follows:</p> <p style="margin-left: 20px;"><input checked="" type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p style="margin-left: 20px;"><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input type="checkbox"/> (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p>		
<p>4. This report contains indications relating to the following items:</p> <p><input checked="" type="checkbox"/> Box No. I Basis of the opinion</p> <p><input type="checkbox"/> Box No. II Priority</p> <p><input checked="" type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p><input type="checkbox"/> Box No. IV Lack of unity of invention</p> <p><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p><input checked="" type="checkbox"/> Box No. VI Certain documents cited</p> <p><input checked="" type="checkbox"/> Box No. VII Certain defects in the international application</p> <p><input checked="" type="checkbox"/> Box No. VIII Certain observations on the international application</p>		
Date of submission of the demand 01.02.2005	Date of completion of this report 26.09.2005	
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Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This report is based on translations from the original language into the following language, which is the language of a translation furnished for the purposes of:
 - ☐ international search (under Rules 12.3 and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4)
 - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)
2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-56 as originally filed

Claims, Numbers

1-49 filed with telefax on 11.08.2005

Drawings, Sheets

1/23-23/23 as originally filed

☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
 - ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
 - ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):

* If item 4 applies, some or all of these sheets may be marked "superseded."

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 40-42 with respect to industrial applicability

because:

☒ the said international application, or the said claims Nos. 40-42 with respect to industrial applicability relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form

☐ has not been furnished

☐ does not comply with the standard

the computer readable form

☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.

☐ See separate sheet for further details

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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	
	No: Claims	1-49
Inventive step (IS)	Yes: Claims	
	No: Claims	1-49
Industrial applicability (IA)	Yes: Claims	1-39, 43-49
	No: Claims	

2. Citations and explanations (Rule 70.7):**see separate sheet**

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and /or

2. Non-written disclosures (Rule 70.9)**see separate sheet**

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

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Supplemental Box relating to Sequence Listing

Continuation of Box I, item 2:

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this report has been established on the basis of:

a. type of material:

- ☒ a sequence listing
☐ table(s) related to the sequence listing

b. format of material:

- ☒ in written format
☒ in computer readable form

c. time of filing/furnishing:

- ☐ contained in the international application as filed
☐ filed together with the international application in computer readable form
☒ furnished subsequently to this Authority for the purposes of search and/or examination
☒ received by this Authority as an amendment on

2. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional observations, if necessary:

see separate sheet

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Re Item I

Basis of the report

1. Sequence listing pages 1-9 filed with the letter of 1.2.2005 do not form part of the application (Rule 13ter.1(f) PCT).

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. Claims 40-42 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

- D1: EP-A-0 786 519 (HUMAN GENOME SCIENCES, INC.) 30 July 1997 (1997-07-30)
- D2: WO 94/06830 A (ALFA LAVAL AGRIC INT AB) 31 March 1994 (1994-03-31)
- D3: WO 02/094868 (CHIRON SPA) 28 November 2002 (2002-11-28)
- D4: MAKOTO KURODA ET AL: "Whole genome sequencing of meticillin-resistant *Staphylococcus aureus* " THE LANCET, vol. 357, 21 April 2001 (2001-04-21), pages 1225-1240, XP004246103
- D5: DATABASE UniProt [Online] 1 December 2001 (2001-12-01), "Hypothetical protein." XP002322488 retrieved from EBI accession no. UNIPROT:Q931M7 Database accession no. Q931M7_STAAM
- D6: DATABASE UniProt [Online] 1 June 2001 (2001-06-01), "Hypothetical protein SA1754." retrieved from EBI accession no. UNIPROT:Q99SU9 Database

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accession no. Q99SU9_STAAN

D7: DATABASE UniProt [Online] 1 June 2001 (2001-06-01), "Fibrinogen binding protein." retrieved from EBI accession no. UNIPROT:Q99UU9 Database accession no. Q99UU9_STAAN

1. The application relates to Staphylococcus "Lectin pathway inhibitor" polypeptides and genes lpi (sequence SEQ ID NO:2 and 3), lpiB (SEQ ID NO:4 and 5) and lpiC (SEQ ID NO:6 and 7) isolated from Staphylococcus aureus strains Mu50 and N315.
2. The term "LPI activity" is not considered to limit the scope of the claim. An activity is considered inherent to the polypeptides of sequences SEQ ID Nos:3, 5 and 7 even if not specifically disclosed. On the other hand, the applicant has not disclosed any of the claimed variants or homologues having such activity.
3. Document D1 discloses Staphylococcus aureus polynucleotides and polypeptides, as well as diagnostic and therapeutic uses thereof, recombinant production and antibodies (see pages 2-26). Table 1 discloses contig 520 (SEQ ID NO:520) as the gene encoding fibrinogen binding protein. SEQ ID NO:520 shows 99.4% sequence identity to SEQ ID NO:4 and 83.2% with SEQ ID NO:6. In the light of D1, claims 1, and 5-49 are not novel and do not comply with the requirements of Article 33(2) PCT.
4. Document D2 discloses a Staphylococcus aureus fibrinogen binding protein showing 100% identity with SEQ ID NO:5 and its encoding polynucleotide which shows 100% identity with SEQ ID NO:4. The claimed embodiments and applications have been as well disclosed in the description pages 1-27. Claims 1 and 5-49 are therefore not novel and do not comply with the requirements of Article 33(2) PCT.
5. Document D3 discloses Staphylococcus aureus polynucleotides and polypeptides, as well as diagnostic and therapeutic uses thereof, recombinant production and antibodies (see pages 2-34). The sequences referred to in D3 have been published on the same date as D3 (28.11.2002) on <http://www.wipo.int/pct/en/sequences/listing.htm> and form part of the state of the art. The polypeptide of sequence SEQ ID NO:1328 shows 99% sequence identity with SEQ ID NO:3. The polypeptide of sequence SEQ ID NO:1102 shows 100%

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identity with SEQ ID NO:5. The polynucleotide of sequence SEQ ID NO:1327 shows 99% identity with SEQ ID NO:1 and 100% identity with SEQ ID NO:2. The polynucleotide of sequence SEQ ID NO:1101 shows 100% identity with SEQ ID NO:4. In the light of D3, claims 1-49 are not novel and do not comply with the requirements of Article 33(2) PCT.

6. Document D4 discloses the whole genome sequencing of *Staphylococcus aureus* strains N315 and Mu50. In the frame of this sequencing proteins identical to SEQ ID Nos: 3 and 5 have been identified in Documents D5, D6, and D7. Claims 22, 23 and 49 are therefore not novel and do not comply with the requirements of Article 33(2) PCT.

6.1. The embodiments relating to polynucleotides and antibodies of the claimed proteins constitute routine manipulations to the skilled person, and therefore, claims 1-21, 24, 27, 30, 33-39, 43-45 and 49 are not inventive and contravene Article 33(3) PCT.

7. For the assessment of the present claims 24-29, 31, 32, 34-37, 39 and 46 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VI**Certain documents cited****Certain published documents**

Application No Patent No	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
EP2004/003398	14/10/2004	31/3/2004	31/3/2003

Re Item VII

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Certain defects in the international application

1. Claims 26, 29, 31, 32 and 47 contain a reference to the description. According to Rule 6.2(a) PCT, claims should not contain such references except where absolutely necessary, which is not the case here.
2. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1-D7 is not mentioned in the description, nor are these documents identified therein.

Re Item VIII

Certain observations on the international application

1. The use of both terms polypeptide and peptide in claims 1, 17, 21-27, 30, 33, 40, 44, 45, 48 and 49 introduces an unclarity in the scope of the claims since there is no clear distinction in the art between a "peptide" and a "polypeptide" (Article 6 PCT).
2. The arbitrary definition "lpi activity" in claims 1, 10, 17, 20, 43-45, 48 and 49 is meaningless to the skilled person and does not convey any technical features to the definition of the subject-matter (Article 6 PCT). Even if such term is defined in the description, the scope of the claims must be clear in itself.
3. The relative terms "part" and "portion" used in claim 1 have no well-recognised meaning and leaves the reader in doubt as to the meaning of the technical features to which they refer, thereby rendering the definition of the subject-matter of said claim unclear (Article 6 PCT). It is unclear what size the part or portion should be and what other technical features it should have.
4. Claim 8 include optional features which do not have any limiting effect in the scope of the claim. The deletion of these features would improve the clarity of the claim as requested according to Article 6 PCT.
5. Claim 22 attempts to define a product, a polypeptide, according to the process to obtain

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it. The method of preparation does not impart any limitation to the product; thereby the claim encompasses other polypeptides than obtained according to the method of the invention. A claim directed to a product according to the process to obtain the same is therefore construed as a claim to the product as such. The product would be better defined in terms of its own structural features such as its amino acid sequence (Article 6 PCT).

6. It is clear from the description that the feature of a protein with lpi activity of sequence SEQ ID Nos:3, 5 or 7 is essential to the definition of the invention. Since independent claim 48 does not contain a reference to the sequences it does not meet the requirement following from Article 6 PCT taken in combination with Rule 6.3(b) PCT that any independent claim must contain all the technical features essential to the definition of the invention.

7. The expression "priming/activating inhibitory polypeptides" in claim 48 is vague and unclear and leaves the reader in doubt as to the meaning of the technical features to which it refers, thereby rendering the definition of the subject-matter of said claim unclear, Article 6 PCT.

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CLAIMS

1. An isolated nucleic acid molecule comprising a nucleotide sequence encoding a peptide or polypeptide having LPI activity, said nucleotide sequence corresponding to a sequence being selected from the group consisting of:
 - a) a nucleotide sequence comprising a part of one of the sequences as depicted in Figure 2a and 2b and identified as SEQ ID NO:2; SEQ ID NO:4; SEQ ID NO:6;
 - 10 b) nucleotide sequences encoding a peptide or polypeptide having LPI activity and having the amino acid sequence depicted in Figure 3 and identified as SEQ ID NO:3, SEQ ID NO:5 or SEQ ID NO:7;
 - c) nucleotide sequences encoding a peptide or
 - 15 polypeptide having LPI activity and having a portion of the amino acid sequence depicted in Figure 3 identified as SEQ ID NO:3, SEQ ID NO:5 or SEQ ID NO:7;
 - d) nucleotide sequences being at least 40% identical to any one of the nucleotide sequences a), b) or c);
 - 20 e) nucleotide sequences hybridizing at stringent conditions with any one of the nucleotide sequences a), b), c) or d), and
 - f) nucleotide sequences complementary to any of the nucleotide sequences a), b), c), d) or e).
- 25 2. An isolated nucleic acid molecule as claimed in claim 1, of which the part of the nucleotide sequence as defined in claim 1 under a) corresponds to nucleotides 1 to 490 of Figure 2a (SEQ ID NO:2).
- 30 3. An isolated nucleic acid molecule as claimed in claim 1 or 2, of which the part of the nucleotide sequence as defined in claim 1 under a) corresponds to nucleotides 41 to 490 of Figure 2a (SEQ ID NO:2).

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4. An isolated nucleic acid molecule as claimed in claim 1, 2 or 3, of which the part of the nucleotide sequence as defined in claim 1 under a) corresponds to nucleotides 125 to 490 of Figure 2a (SEQ ID NO:2).

5 5. An isolated nucleic acid molecule as claimed in claim 1, of which the part of the nucleotide sequence as defined in claim 1 under a) corresponds to nucleotides 1 to 490 of lpi-B (SEQ ID NO:4) or lpi-C (SEQ ID NO:6) in Figure 2b.

10 6. An isolated nucleic acid molecule as claimed in claim 1 or 2, of which the part of the nucleotide sequence as defined in claim 1 under a) corresponds to nucleotides 41 to 490 of lpi-B (SEQ ID NO:4) or lpi-C (SEQ ID NO:6) in Figure 2b.

15 7. An isolated nucleic acid molecule as claimed in claim 1, 2 or 3, of which the part of the nucleotide sequence as defined in claim 1 under a) corresponds to nucleotides 125 to 490 of lpi-B (SEQ ID NO:4) or lpi-C (SEQ ID NO:6) in Figure 2b.

20 8. An isolated nucleic acid molecule as claimed in claims 1-7, wherein the nucleotide sequence as defined in claim 1 under d) is at least 40%, at least 50%, preferably at least 60% or at least 70%, more preferably at least 75%, even more preferably at least 80%, most preferably at least 90% identical to any one of the nucleotide sequences a, b or c.

25 9. An isolated nucleic acid molecule as claimed in claims 1-8, wherein the stringent conditions are constituted by overnight hybridization at 42°C in 5xSSC and washing at 65°C at 0.1xSSC.

30 10. An isolated nucleic acid molecule as claimed in claims 1-9, wherein a portion of the amino acid sequence as defined in claim 1 under c) constitutes alone or with other portions of the amino acid sequence the region(s) of the

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peptide or polypeptide having LPI activity that lead to biological activity.

11. An isolated nucleic acid molecule as claimed in claims 1-10, which nucleic acid is DNA, RNA or cDNA.

5 12. Recombinant vector comprising an isolated nucleic acid molecule as claimed in claims 1-11.

13. Method for making a recombinant vector comprising inserting at least one isolated nucleic acid molecule as claimed in claims 1-11 into a vector.

10 14. Bacteriophage comprising an isolated nucleic acid molecule as claimed in claims 1-11.

15 15. Recombinant host cell or organism comprising an isolated nucleic acid molecule as claimed in claims 1-11, a vector as claimed in claim 12 or a bacteriophage as claimed in claim 14.

16. A recombinant host cell as claimed in claim 15, wherein the host cell is selected from the group consisting of the bacteria *Escherichia coli*, *Bacillus subtilis*, *Staphylococcus aureus*, the yeasts *Saccharomyces cerevisiae*, *Pichia pastoris*, *Candida*, insect cells of the *Drosophila* system and the Baculovirus system, the mammalian cells monkey COS, hamster CHO, hamster BHK, hamster RBL-2H3, human 293, human 3T3, human HeLa, human U937, human HL-60, human Jurkat cells, mouse L cells.

25 17. Method for producing a recombinant peptide or polypeptide having LPI activity, comprising culturing a recombinant host of claim 15 or 16 under conditions such that said peptide or polypeptide is expressed and recovering said peptide or polypeptide.

30 18. Method as claimed in claim 17, wherein the host cell is an *Escherichia coli* cell.

19. Method as claimed in claim 17, wherein the host cell is a *Staphylococcus aureus* cell.

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20. Method as claimed in claim 19, wherein the *Staphylococcus aureus* cell is from a strain that already produces an endogenous protein having LPI activity (LPI).

21. Method for producing a synthetic peptide or
5 polypeptide having LPI activity, comprising deducing the amino acid sequence encoded by a nucleic acid molecule as claimed in claims 1-11 and synthetically producing a peptide or polypeptide having the said amino acid sequence.

22. Peptide or polypeptide having LPI activity
10 obtainable by any one of the methods as claimed in claims 17-21.

23. Peptide or polypeptide as claimed in claim 22 having the amino acid sequence depicted in Figure 3 and identified as SEQ ID NO:3, SEQ ID NO:5 or SEQ ID NO:7.

15 24. Peptide or polypeptide as claimed in claim 22 or 23 for use in diagnosis, prophylaxis or therapy.

25. Peptide or polypeptide as claimed in any one of the claims 22-24 for use in the treatment of acute and chronic inflammation reactions.

20 26. Peptide or polypeptide as claimed in any one of the claims 22-24 for use in the treatment diseases in Table 2.

27. Use of the peptide or polypeptide as claimed in claim 22 or 23 for the manufacture of a therapeutic
25 preparation for diagnosis, prophylaxis or therapy.

28. Use as claimed in claim 27 for the treatment of acute and chronic inflammation reactions.

29. Use as claimed in claims 27 or 28 for the treatment of diseases in Table 2.

30 30. A therapeutic composition comprising a suitable excipient and the peptide or polypeptide as claimed in claim 22 or 23.

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31. A composition as claimed in claim 30 for treating acute and chronic inflammation reactions as listed in Table 2.

32. A composition as claimed in claim 30 for treating diseases in Table 2.

33. An antibody or biologically active fragment thereof specifically directed to the peptide or polypeptide as claimed in claim 22 or 23.

34. An antibody as claimed in claim 33 for use in diagnosis, prophylaxis or therapy.

35. An antibody as claimed in claim 33 or 34 for use in the treatment of staphylococcus infection.

36. Use of an antibody as claimed in claim 33 for the manufacture of a therapeutic preparation for diagnosis, prophylaxis or therapy.

37. Use as claimed in claim 36 for the treatment of staphylococcus infection.

38. Therapeutic composition comprising a suitable excipient and one or more antibodies as claimed in claim 33 and/or biologically active fragments thereof.

39. An isolated nucleic acid molecule as claimed in any one of the claims 1-11 for use in gene therapy.

40. Method for treating a subject suffering from inflammation by administering a therapeutically effective amount of a peptide or polypeptide as claimed in claim 22.

41. Method for gene therapeutically treating a subject suffering from inflammation by administering a therapeutically effective amount of a nucleic acid molecule as claimed in claims 1-11.

42. Method for treating a subject suffering from staphylococcus infection by administering a therapeutically effective amount of an antibody and/or biologically active fragment thereof as claimed in claim 33.

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43. Method for isolating from an organism a gene encoding a protein having LPI activity, comprising screening of a genomic or cDNA library of that organism with a probe that is capable of hybridising with the nucleic acid molecule
5 as claimed in claims 1-11, isolation of the positive clones, and testing whether the positive clones show LPI activity.

44. Method for identifying nucleic acid sequences encoding a peptide or polypeptide having LPI activity, comprising comparison of the sequence as depicted in Figures
10 2a and 2b identified by SEQ ID NO:2, SEQ ID NO:4 or SEQ ID NO:6 with the nucleic acid or protein sequence information contained in a database and selecting sequences that are at least 60% identical to the sequences as depicted in Figures 2a and 2b and identified by SEQ ID NO:2, SEQ ID NO:4 or SEQ
15 ID NO:6.

45. Method for identifying amino acid sequences of a peptide or polypeptide having LPI activity, comprising comparison of the sequences as depicted in Figure 3 and identified by SEQ ID NO:3, SEQ ID NO:5 or SEQ ID NO:7 with
20 the nucleic acid or protein sequence information contained in a database and selecting sequences that are at least 40% identical to the sequences as depicted in Figure 3 and identified by SEQ ID NO:3, SEQ ID NO:5 or SEQ ID NO:7.

46. Micro-organism harboring a nucleic acid molecule
25 as claimed in claims 1-11 for use as a medicament for the treatment of acute and chronic inflammation reactions.

47. Micro-organism as claimed in claim 43 for treating diseases listed in Table 2.

48. Method for producing peptides or polypeptides
30 having LPI activity, comprising culturing wild-type, non-recombinant, *Staphylococcus* strains that produce endogenous priming/activation inhibitory peptides or polypeptides and recovering same.

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49. Peptide or polypeptide having an amino acid sequence that is at least 40% homologous to the amino acid sequence depicted in Figure 3 (SEQ ID NO:3; SEQ ID NO:5; SEQ ID NO:7) and having at least LPI activity.

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P.O. BOX 18558, NL-2502 EN THE HAGUE, 23 November 2004

Our ref.: L/2BD29/LB/2

Your ref.: --

Re.: International Patent Application No. PCT/EP04/007606
 in the name of: UMC Utrecht Holding B.V.

In the above identified application I herewith request the
 correction of the address of the applicant pursuant to Rule 88
 EPC. The correct address should be:

UMC Utrecht Holding B.V.

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